REMARKS

The present invention, as recited by claims 1 – 16, as amended, provides a unique means for treating onychomycosis. Generally stated, there is provided in accordance with applicant's amended claims, a nail formulation and a method for the topical treatment of nail infections. The nail formulation comprises, as an active ingredient, at least one species selected from the group consisting of 2,2' -(alkyldioxy) bis- (alkyl-1, 3,2-dioxaborinane) and 2,2'-oxybis(alkyl-1, 3,2-dioxaborinane). More specifically, the composition comprises, as an active ingredient, at least one member selected from the group consisting of 2,2' - (1-methyltrimethylene dioxy) bis - (4-methyl-1, 3, 2-dioxaborinane) and 2,2' - oxybis (4, 4, 6 - trimethyl-1, 3, 2-dioxaborinane). The invention also comprises a method of treating onychomycosis by topical application of a nail formulation containing, as an active ingredient, at least one member selected from the group consisting of 2,2' - (1-methyltrimethylene dioxy) bis - (4-methyl-1, 3, 2-dioxaborinane) and 2,2' - oxybis (4, 4, 6 - trimethyl-1, 3, 2-dioxaborinane). The application of this nail formulation effectively kills the most common pathogen causing onychomycosis, *Candida albicans*. Importantly it has been determined by *in vivo* tests on volunteers that the nail formulations defined by applicant's claims, as amended, achieve efficacy in the treatment of onychomycosis without skin irritation or noticeable side effects.

Applicant gratefully acknowledges the Examiner's statement that a significant nail formulation would be allowable. In order to comply with the Examiner's suggestion, claims 1-14 have been amended for the sake of clarity to replace the phrase "A topical composition for treatment of nail infections" with the suggested phrase -- A nail formulation for the topical treatment of nail infections --.

Claims 1-5 and 11-16 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Application 5,972,317 to Sorenson et al. in view of U. S. Patent Application 5,874,476 to Hsu et al., in further view of U.S. Patent Application 4,608,440 to Saischek et al.

Sorenson discloses a nail-permeable medication means for delivering a medicament through nails claws, hoofs or other similar hardened tissue of dermal derivation. The composition for treating the diseased nails and other dermal tissue comprises a proteolytic enzyme and a medicament. The medicament is selected for treatment of a particular disease condition. Examples of medicaments which may be used in the nail-permeable medication means include antibacterial, anti-viral, antifungal and other antimicrobial compositions. Such drugs may also be ionic, anionic, nonionic, cationic, zwitterionic, or ampholytic. Suitable drugs for use in the nail-permeable medication means include ciclopirox olamine, miconazole, tolnaftate, terbinafme, amorolfm and econazole. Soreson et al. does not disclose the use of 2,2' -(alkyldioxy) bis- (alkyl-1, 3,2-dioxaborinane) and 2,2'-oxybis(alkyl-1, 3,2-dioxaborinane) in the nail permeable medication. In addition, Sorenson et al does not disclose the use of boric acid as an antifungal agent, but does disclose the use of boric acid in the formulation of a solution containing the nail-penetrating enzyme, papain.

Hsu et al. discloses a method of using an antimicrobial agent to inhibit the growth of microorganisms in, at, or on a locus subject to microbial attack. The antimicrobial agent described by Hsu et al. consists of certain dihaloformaldoxime carbamates. Along with numerous other materials Hsu discloses that the anti-microbial composition may be added to toiletries, shampoos, cosmetics and soaps. The carbamates can be combined with one or more other antimicrobial agents. Preferred known antimicrobial agents to be combined with the carbamates are methylenebis (thiocyanate); 5-chloro-2-methyl-4-isothiazolin-3-one; 2-methyl-4-isothiazolin-3-one; as 2-n-octyl-4-isothiazolin-3-one; 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one; 1,2-benzisothiazolin-3-one; zinc 2-pyridinethiol-1-oxide; sodium 2-pyridinethiol-1-

oxide; N'-3, 4-dichlorophenyl! -N, N-dimethylurea; 3-iodopropargyl-N-butylcarbamate; 10,10'-oxybisphenoxyarsine; 2-(thiocyanomethylthio) benzothiazole; 3-bromo-1-chloro-5, 5-dimethylhydantoin; 2,2-dibromo-3-nitrilopropionamide; pentane-1, 5-dial; and 2-bromo-2-nitro-1, 3-propanediol. However, Hsu et al. also discloses that the carbamates can be combined with numerous other known microbial agents which includes 2,2'-oxybis(4,4,6-trimethyl-1, 3, 2 dioxaborinane and 2,2'-(1-methyltrimethylenedioxy) bis (4-ethyl-1, 3,2-diozaborinane. Thus, Hsu et al teaches a combination of a carbamate alone or with another antimicrobial agent inhibits the growth of microorganisms.

On the other hand, there is no suggestion in Hsu et al. that the two anti-microbial agents called for by applicant's claims could be used in the treatment of nail infections. This is the case even though Hsu et al. discloses over one hundred anti-microbial agents that may be combined with a carbamate to inhibit microbial growth. It is highly unlikely that one skilled in the art would have selected 2,2'-oxybis(4,4,6-trimethyl-1, 3, 2 dioxaborinane and 2,2'-(1-methyltrimethylenedioxy) bis (4-ethyl-1, 3,2-diozaborinane out of the multitude of compounds disclosed by Hsu et al. as a nail formulation and method for the topical treatment of nail infections, especially considering the common use of these compounds. These two compounds are the active ingredients of Biobor, a fungicide used in the fuel tanks and fuel lines of vehicles, farm equipment and industrial engines to prevent the growth of microbial organisms which could interfere with the use of non-gasoline fuels. The Material Safety Data Sheet for Biobor lists the hazards of the fuel additive. Hazards listed by the reference include, "SKIN CONTACT: May cause slight to mild irritation". In addition, the Material Safety Data Sheet states: "Prolonged or repeated contact may dry the skin and lead to irritation (i.e. dermatitis)". Clearly, these statements on the Material Safety Data Sheet point away from the use of 2,2' - (1-methyltrimethylene dioxy) bis - (4-methyl-1, 3, 2-dioxaborinane) and 2,2' - oxybis (4, 4, 6 - trimethyl-1, 3, 2-dioxaborinane) as a nail formulation and method for the

topical treatment of nail infections, as defined by present claims 1-5 and 11-16. It is therefore submitted that the common use of 2,2'-oxybis(4,4,6-trimethyl-1, 3, 2 dioxaborinane and 2,2'-(1-methyltrimethylenedioxy) bis (4-ethyl-1, 3,2-diozaborinane, and information on their safety actually teach away from the use of these compositions in the nail formulation of present claims 1-14 and as being important ingredients in the method for topical treatment of nail infections defined by present claims 15-16.

Saischek et al. discloses a composition which contains certain 1,3,2-dioxyborinane bonded in the 2-position to an organo-tin compound. This composition was found to inhibit the growth of various bacteria, fungus algae, and insects. In several examples, Saischek et al demonstrate the growth inhibition of bacteria, fungus and insects on plants. However, there is no disclosure or suggestion in Saischek et al concerning the toxicity of the 1,3,2-dioxyborinane compounds to the plants at the concentrations used. In addition, Saischek et al do not suggest that the disclosed composition would be suitable for use on animals. Furthermore, the common use of 2,2'-oxybis(4,4,6-trimethyl-1, 3, 2 dioxaborinane and 2,2'-(1-methyltrimethylenedioxy) bis (4-ethyl-1, 3,2-diozaborinane, taken alone or in light of information on their safety, would teach away from their use as a nail formulation and method for the topical treatment of nail infections.

Applicant respectfully disagrees with the Examiner that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Sorenson et al., Hsu et al and Saischek et al. There is clearly no disclosure or suggestion in any of these patents concerning the use of 2,2'-oxybis(4,4,6-trimethyl-1, 3, 2 dioxaborinane and 2,2'-(1-methyltrimethylenedioxy) bis (4-ethyl-1, 3,2-diozaborinane as a nail formulation in the topical treatment of nail infections. Although both Hsu et al and Saischek et al disclose the use of 1, 3, 2-dioxaborinane as an antimicrobial agents, the common use and safety data of Biobor would teach against the use of 1, 3, 2-dioxaborinane in the treatment of animal

antimicrobial infections. Thus, there would exist no motivation to combine the teaching of Hsu et al and Saischek et al with Sorenson et al. et al, because Sorenson et al. discloses the use of proteolytic enzymes for the delivery of a medicament through nails, claws, hoofs, or other hardened tissues. Sorenson discloses several suitable medicaments to be used with the nail formulation including ciclopirox olamine, miconazole, tolnaftate, terbinafme, amorolfm and econazole. Each of these has previously been used as anti-fungal medicaments for humans. There is no suggestion in Sorenson et al. for the use of an anti-microbial medicament that has not previously been extensively used on humans. One skilled in the art would not be motivated to use the proteolytic enzymes of Sorenson et al to enhance the effectiveness of 2,2' - (1-methyltrimethylene dioxy) bis - (4-methyl-1, 3, 2-dioxaborinane) and 2,2' - oxybis (4, 4, 6 - trimethyl-1, 3, 2-dioxaborinane) in the treatment of nail and skin infections. Indeed, one skilled in the art would not consider these compounds to be suitable for use in the treatment of nail and skin fungus. The primary use of 2,2' - (1-methyltrimethylene dioxy) bis - (4-methyl-1, 3, 2-dioxaborinane) and 2,2' - oxybis (4, 4, 6 - trimethyl-1, 3, 2-dioxaborinane) is that of a fuel additive, which prevents microbial growth that could interfere with the use of non-gasoline fuels. In addition, these two compounds cause skin irritations at working concentrations. Thus Applicant respectfully submits that the present nail formulation and method for its application, as delineated by amended claims 1-5 and 11-16, is not obvious over Sorenson et al. in view of Hsu et al in further view of Saischek et al.

Accordingly, reconsideration of the rejection of claims 1-5 and 11-16 under 35 U.S.C 103(a) as being unpatentable over the combination of Sorenson et al., Hsu et al and Saischek et al. is respectfully requested.

Claims 1 – 16 were rejected under 35 U.S.C. 103(a) as being unpatentable over U. S. Patent No. 5,346,692 to Wollrab et al. in view of U.S. Patent No. 5,874,476 to Hsu et al. in

further view of U.S. Patent No. 4,608,404 to Saischek et al.

Wohlrab et al. discloses a nail lacquer for treatment of onychomycosis. The composition for the treatment of toenail fungus comprises a polymeric film forming agent, at least one antimycotically active substance, urea and a solvent. The antimycotically active substances include clotrimazole, bifonazole, butaconazole, chlordantoin, chlormidazole, cloconazole, enilconazole, fenticonazole, isoconazole, ketoconazole, omoconazole, oxiconazole nitrate, and sulconazole. The antimycotically active substance and the urea are liberated from the lacquer when the lacquer is applied to the nail. There is no suggestion in Wollrab et al. to use an antimycotically active substance that is not presently commonly used on humans.

Applicant respectfully disagrees with the Examiner that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Wollrab et al., Hsu et al., and Saischek et al. Like Sorenson et al., Wohlrab et al discloses a nail formulation and method to facilitate the treatment of onychomycosis by anti-fungal medicaments. Each of Sorenson et al. and Wohlrab et al. disclose anti-fungal medicaments that have been commonly used on humans. Neither Sorenson et al. nor Wohlrab et al. suggest the use of a medicament that is not commonly used on humans.

One skilled in the art would not think to use the nail lacquer of Wohlrab et al. to enhance the effectiveness of 2,2' - (1-methyltrimethylene dioxy) bis - (4-methyl-1, 3, 2-dioxaborinane) and 2,2' - oxybis (4, 4, 6 - trimethyl-1, 3, 2-dioxaborinane) in the treatment of nail and skin infections. Indeed, one skilled in the art would not consider these compounds to be suitable for use in the treatment of nail and skin fungus. The primary use of 2,2' - (1-methyltrimethylene dioxy) bis - (4-methyl-1, 3, 2-dioxaborinane) and 2,2' - oxybis (4, 4, 6 - trimethyl-1, 3, 2-dioxaborinane) constitutes that of a fuel additive, operative to prevent microbial growth that could interfere with the use of non-gasoline fuels. Significantly, these

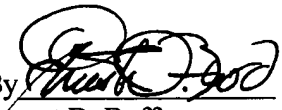
two compounds are said to cause skin irritations at working concentrations. For these reasons, it would not be obvious to one skilled in the art to combine Wohlrab et al.'s enhanced delivery method for treating onychomycosis with the 1,3,2-dioxyborinane compounds disclosed in Saischek et al. and the carbamate mixture of Hsu et at. to obtain a nail formulation for the topical treatment of a nail infection, as called for by applicant's claims.

Accordingly, reconsideration of the rejection of claim 1-16 under 35 U.S.C 103(a) as being unpatentable over the combination of Wollrab et al., Hsu et al. and Saischek et al. is respectfully requested.

CONCLUSION

In light of the amendments to the claims and the remarks set forth above, it is submitted that the subject matter of present claims 1-16 patentably defines over the art applied, and that the present application is in allowable condition.. Accordingly, reconsideration of the rejection of present claims 1 – 16 and their allowance are earnestly solicited.

Respectfully submitted,
James E. Brehove

By 
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